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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/11/2010 has been entered.

Applicants' amendments and arguments filed March 11, 2010 have been received and entered. Claim 1 has been amended, while claims 2-5, 9-10, 12-28 have been canceled. Claims 1, 6-8 and 11 are pending.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 was acknowledged.

Claims 1, 6-8 and 11 are under consideration.

Withdrawn -Claim Rejections - 35 USC § 112

Claims 1, 6-8 and 11 were rejected under 35 U.S.C. 112, first paragraph, because the specification, because the specification fails to provide an enablement for the full scope of the claimed invention. Applicants have amended claims to limit the indicated scope to a method of determining that a pregnant woman is at risk of developing pre-eclampsia or whether that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring plasma concentration of asymmetric dimethylarginine (ADMA) in a pregnant woman at risk of developing pre-eclampsia or her fetus being at risk of developing IUGR at a stage of pregnancy from 23 to 25 weeks gestation; and (b) plasma ADMA level in said women greater than 1.5 microM/L indicates that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR. Therefore, rejection of claims 1, 6-8 and 11 are hereby withdrawn.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1 and 7 were rejected under 35 U.S.C. 103(a) as being unpatentable over Boger (WO 2002/14873, 2/21/2002, IDS), Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record). Applicants' argument that neither Boger nor Holden disclose measuring ADMA in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation is persuasive. Therefore, the previous rejections of claims 1 and 7 are hereby withdrawn. Applicants' arguments with respect to the withdrawn rejections are thereby rendered moot. The claims are however subject to new rejections over prior art of record summarized by the reference of Ellis et al that teaches measuring ADMA in a plasma sample taken from a pregnant woman at a stage of pregnancy from 24 to 32 weeks gestation, as set forth below.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6-7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record), Ellis et al (Acta. Obstr. Gynecol. Scand. 2001: 80, 602-608, IDS) and Boger (WO 2002/14873, 2/21/2002, IDS).

Claims are directed a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation; and (b) determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA in the plasma sample is greater than 1.5 gmol/L. Claim 6 limits the method of claims 1, wherein determining that the woman is at risk of developing pre-eclampsia or determining that her fetus is at risk of developing IUGR comprises determining that the woman's ADMA level is at least 3 times the normal pregnancy level.

Holden et al teach a method comprising (a) measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at different stage of pregnancy; and

(b) determining the level of ADMA in the plasma sample. It is noted that Holden et al also determined the level of ADMA to be around 0.52 μmol/L to 1.17 μmol/L during second trimester. This would meet the claim limitation of measuring pregnancy at different stage of pregnancy (including 23-25 weeks) that is embraced by the teaching of Holden (see page 553, Figure 1 B). It is further disclosed that pregnant woman have pre-eclampsia if ADMA in the plasma sample is greater than 1.25 gmol/L (see figure 1A). Therefore, any ADMA level greater than 1.25 gmol/L would also have PE meeting the limitation of the claim. It is further noted that Holden et al conclude that during later stage of pregnancy circulating concentrations increase and, when pregnancy is complicated by preeclampsia. Thus, method of Holden is primarily directed to study the role for ADMA in the changes in blood pressure seen in both normal and preeclampsia pregnancy (see abstract and page 555, col. 1, para. 4). While Holden et al teach a method of measuring ADMA level at least in pregnant women and reported pre-eclampsia if ADMA in the plasma sample is greater than1.25 gmol/L, but differ from claimed invention by not measuring the ADMA level in women at 23 to 25 weeks gestation.

However, such was disclosed by Ellis et al , who reported measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation; and (b) determining the level of ADMA in the plasma sample. It is disclosed that plasma concentrations of both asymmetric and symmetric dimethylarginine are significantly elevated both in mild and severe preeclarnpsia during pregnancy from 24 to 32 weeks gestation that includes 24 and 25 weeks gestation (see abstract, figure 1 and 2). Ellis et al further contemplate studying ADMA and SDMA level early in the pregnancy in order to ascertain if levels rise early enough to predict preeclampsia (see page 607, col. 1, para. 1). While Ellis et al teach a method of measuring ADMA level in women at 23 to 25 weeks gestation having preeclampsia, but differ from claimed invention by not measuring the ADMA level in non pre screened pregnant women.

Boger et al cure the deficiency by teaching a method of detecting the risk of developing a disease including pre-eclampsia that is associated with NO metabolism by (a) measuring the level of ADMA and SDMA (see claims 1 and 9). Boger et al also disclose that preeclampsia is a disease of the NO metabolism leads to constriction of arteries which induces high blood pressure in the mother and poses a risk to the unborn child due to reduced placental perfusion (see page 2)

With respect to claim 7 and 8, Boger et al contemplate measuring the ratio of ADMA to SDMA in the plasma of the patient (see claim 14, 20 and 21). It is also disclosed that subject suffering from chronic conditions (CHF, example 4) show ADMA concentration of 4.1 μM/L as compared to 1.0 μM/L in normal subject.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Holden of measuring the ADMA level in detecting the risk of developing a disease including pre-eclampsia in the mother due to reduced placental perfusion as disclosed by Boger using the known method disclosed by Holden and Ellis. It would have been *prima facie* obvious to one of ordinary skill in the art to combine the known methods of Holden, Ellis and Boger to measure the ADMA level in a pregnant women at a stage of pregnancy "comprising" 23-25 and determine the level of ADMA to detect the risk of developing of pre-eclampsia particularly since both Holden and Ellis generally embraced the potential of measuring ADMA level to determine the risk of developing pre-eclampsia. Other limitations of measuring ADMA level that is at least 3 times or ADMA/SDMA level 5 times than the normal pregnancy level would be implicit in the method taught by the combination of references and therefore would be obvious variables when measuring the level of ADMA or SDMA in pregnant women predisposed to develop PE as disclosed by Ellis. One who would have practiced the invention would have had reasonable expectation of success since Ellis and Holden both taught method to measure ADMA level in the plasma of subject to determine if the subject is at risk of developing PE, while combining the teaching Holden, Ellis with Boger would have resulted in a determining the level of ADMA that is greater then 1.250 μM/L to establish risk of developing pre-eclampsia.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record), Ellis et al (Acta. Obstr. Gynecol. Scand. 2001: 80, 602-608, IDS) and Boger (WO 2002/14873, 2/21/2002, IDS) as applied to claims 1, 6-8 above, and further in view of Albaiges et al (Obstet Gynecol 2000;96:559-64, IDS).

The teachings of Holden et al, Ellis et al and Boger were described above and relied in same manner here. The combination of art teach a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises measuring asymmetric dimethylarginine (ADMA) in a plasma sample taken from a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation, but differ from claimed invention by not disclosing use of Doppler waveform analysis of uterine arteries and/or flow mediated dilatation of the brachial artery in the women.

However, use of Doppler wave form to predict PE in pregnant women was known and routinely used by one of ordinary skill in the art. For instance, Albaiges et al discloses color doppler of uterine artery imaging of women with singleton pregnancies at 23 weeks to determine bilateral uterine artery notches, left and right uterine artery pulsatility indices (PI) for predicting preeclampsia and delivery of small-for-gestational-age infants (See abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art seeking to predict risk of developing PE would combine the respective teachings of Holden et al, Ellis et al and Boger by modifying the method to further include Doppler waveform analysis of uterine arteries to determine if a pregnant woman is at risk of developing PE as disclosed by Albaiges et al, with a reasonable expectation of success. A person of skill in the art would have been motivated to modify the method of combination references by further conducting Doppler analysis as disclosed by Albaiges et al, as a matter of design choice, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One of ordinary skill in the art would be motivated to do so as Albaiges et al teaches use of color doppler of uterine artery imaging of women with singleton pregnancies at 23 weeks to predict preeclampsia in women risk of developing PE (supra) . One of skill in the art would have been expected to have a reasonable expectation of success in determining if a pregnant woman is at risk of developing pre-eclampsia or IUGR by measuring ADMA and color doppler imaging because the art teaches the successful detection of PE using Doppler waveform analysis of uterine arteries. It should be noted that the *KSR* case forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25,

2007) (citing *KSR*, 82 USPQ2d at 1396) (available at http: www. uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf).

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anoop Singh/
Examiner, Art Unit 1632